UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,173	12/10/2004	Didier Hoarau	1017753-000201	5720

21839 7590 05/08/2008
BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER	
PALENIK, JEFFREY T	

ART UNIT	PAPER NUMBER
1615	

NOTIFICATION DATE	DELIVERY MODE
05/08/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ADIPFDD@bipc.com

Office Action Summary	Application No.	Applicant(s)	
	10/518,173	HOARAU ET AL.	
	Examiner	Art Unit	
	Jeffrey T. Palenik	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33,43,44 and 52-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33,43,44 and 52-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10 Mar 2005 and 5 Jan 2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Remarks

The Examiner thanks the Applicants for their timely reply filed on 7 January 2008, in the matter of 10/518,173.

Applicants' arguments filed 4 January 2008 have been fully considered but they are not persuasive.

Applicants' election **without traverse** of Group I, claims 1-33, 43, 44 and 52-57, is acknowledged.

Though made **without traverse**, the Examiner withdraws the requirements for the elections of species.

The Examiner further acknowledges paragraph 1 on page 14 of Applicants' response. At the time the Requirement for Restriction was submitted for review, approval and subsequent mailing to Applicants, implementation of said verbiage informing Applicants as to the proposed changes to Claims and Continuations Final Rule practice was still required. As Applicants correctly state, the proposed changes did not go into effect as of 1 November 2007, and therefore the aforementioned verbiage on page 7 of the previous action is moot.

The claims 1-33, 43, 44 and 52-57 are presented and represent all claims under consideration.

Information Disclosure Statement

Two Information Disclosure Statements filed 10 March 2005 and 5 January 2007

are acknowledged and have been reviewed.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-11, 13-33, 43, 44 and 52-57 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4-14, 16, 17, 19-39, 49 and 50 of copending Application No. 10/458,324. Although the conflicting claims are not identical, they are not patentably distinct from each other because each are drawn to stealth lipid nanocapsules comprising a liquid or semi-liquid lipid core, the capsules further comprising at least one of each hydrophilic and lipophilic surfactants and an amphiphilic derivative of polyethylene glycol. Further, limitations recited in the claims of the '324 application encompass and/or are encompassed by the

limitations of the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-33, 43, 44 and 52-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "in nature" in claims 1, 22, 28, and 30, is a relative term which renders the claim indefinite. The term "in nature" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The parameters that are rendered indefinite by the above term are the degree to which either a hydrophilic or lipophilic surfactant is lipidic.

The limitation "wherein the molar mass of poly(ethylene glycol) component is greater than or equal to 1000 g/mol" as recited in claim 1 is indefinite because it is unclear whether said amount is pertaining to the amphiphilic derivative or the total nanocapsules.

Lecithin is another name for phosphatidylcholine (see p. 711 of the Merck index, 9th Ed.). Therefore, it is unclear what Applicants intend to convey by the limitation

"phosphatidylcholine proportion of which is at least equal to 95%" as recited in claim 3, and "phosphatidylcholine proportion of which is at least equal to 99%" as recited in claim 52. Therefore, given its broadest reasonable interpretation and for the purposes of examination on the merits, the Examiner interprets the terms lecithin and phosphatidylcholine to be synonymous with one another to the point lecithin is 100% phosphatidylcholine.

The terms "type" and "types" as recited in claims 9, 11 and 24, are indefinite because it is unclear exactly what "type" of each claims' respective compound is being claimed. Per MPEP 2173.05(b)(E), the term "type" extends the scope of an otherwise definite expression such that it renders it indefinite.

The recitation "allows it to be anchored" in deference to the anchoring of the hydrophilic component to the outer lipid envelope, in claim 11, is indefinite because it is unclear whether or not the limitation is part of the instant invention.

The term "mainly" in claim 28 is a relative term which renders the claim indefinite. The term "mainly" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The parameter rendered indefinite by the above term is the degree to which the anticancer active principle(s) is lipophilic.

The remaining claims are rejected as being dependent from the above rejected claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-33, 43, 44 and 52-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heurtault et al. U.S. Pre-Grant Publication No. 2003/0152635 (this is the English equivalent of WO 01/64328), in view of Önyüksel et al. (USPN 6,217,886), BASF Technical Information packet, The Merck Index and Merriam-Webster Online Medical Dictionary.

The instant claims are drawn to lipid nanocapsules comprising a liquid or semi-liquid lipid core and an outer lipid envelope which comprises a lipid-based, hydrophilic surfactant a lipid-based lipophilic surfactant and an amphiphilic derivative of polyethylene glycol (PEG) wherein the PEG component of the derivative is greater than or equal to 1,000 g/mol. Dependent claim 2 further limits the molar mass of the PEG component to 2,000 g/mol. Claims 3 and 52 further limit the lipophilic surfactant to

lecithin, wherein the composition dedicated to phosphatidylcholine is 95% or greater and 99% or greater, respectively. Claims 4 and 53 further limit the lipophilic surfactant to one having a gel/liquid transition temperature of at least 25°C and 37°C, respectively. Claims 5 and 6 further limit the lipophilic surfactant to hydrogenated soy phosphatidylcholine (HSPC), distearoyl phosphatidylcholine (DSPC), and dipalmitoyl phosphatidylcholine (DPPC). Claim 7 further limits the composition of claim 1 such that the lipophilic surfactant comprises 5-30 mol% of the outer lipid envelope. Claims 8 and 9 further limit the hydrophilic surfactant to a non-ionic surfactant such as polyethylene glycol-660 12-hydroxystearate. Claims 10 and 54, further limit the composition of claim 1 such that the hydrophilic surfactant comprises 60-90 mol% and 80 mol% of the outer lipid envelope, respectively. Claims 11-15 further limit the amphiphilic derivative of the composition. Claim 55 further limits the composition of claim 15 such that the amphiphilic PEG derivative comprises 1-10 mol% of the outer lipid envelope. Claims 16 and 56 further limit the nanocapsule composition such that the lipid core comprises 20-60% by weight and 25-50% by weight of the total weight of the nanocapsules, respectively. Claims 17-20 further limit the composition of the lipid core to ethyl palmitate, ethyl oleate, ethyl myristate, isopropyl myristate and octyldodecyl myristate. Claims 21 and 57 further limit the diameter of the individual nanocapsules to a range of 50-150 nanometers (nm) and 80-120 nm, respectively. Claim 22 further limits the composition of claim 1 such that the outer surface of said envelope is hydrophilic and the core is lipophilic. Claims 23 and 24 further limit the nanocapsules such that their surfaces carry target-specific ligands. The limitations of claims 25 and 26 do not further

limit the composition of claim 1. Rather the limitations recite intended future use, which per MPEP 2111, hold no patentable weight. Therefore, claims 25 and 26 are interpreted the same as claim 1. Claims 27-33 further limit the nanocapsule composition to anti-cancer and anti-inflammatory active principles. Claims 43 and 44 recite a pharmaceutical composition which comprises the nanocapsule composition of claim 1 and carried by a colloidal aqueous suspension.

Heurtault et al. teaches lipid nanocapsules having a liquid or semi-liquid lipid core and an outer lipid envelope, wherein said nanocapsules have an average diameter ranging in preferences from less than 150 nm down to less than 50 nm (claim 1). Claim 4 teaches that the lipid core consists of a fatty substance such as a triglyceride or a fatty acid ester comprising 20-60% and preferably 25-50% by weight of the nanocapsules. Claim 5 teaches the lipid core as consisting of capric and caprylic triglycerides and claim 6 teaches that the fatty acid esters of the instant claim 20 constitute the lipid core of the nanocapsules. Claim 10 teaches that the lipid surfactant is lecithin whose phosphatidylcholine proportion is between 40-90%. The lipophilic surfactant is taught as being solid at 20°C and liquid at about 37°C [0018]. Heurtault teaches Lipoid® S 75-3, which is a soybean lecithin (e.g. a soy phosphatidylcholine lipophilic) surfactant which is used to make nanocapsules [0046]. Heurtault also teaches Solutol® HS 15 at [0047] as the commercial name for the compound polyethylene glycol-660 12-hydroxystearate (stated incorrectly in the reference as polyethylene glycol-660 ***2-hydroxystearate***; see BASF NPL) which acts as a nonionic hydrophilic surfactant in the formulation. Pharmaceutically active principles are taught as being either soluble or dispersible in the

lipid core of the nanocapsule [0055] or as being water-soluble and attached to the surface of the nanocapsules, thereby making the outer lipid envelope, capable of being hydrophilic in nature. Water-soluble pharmaceutically active principles bound to the surface of the nanocapsules (i.e. surface-specific ligands; see also definition of "ligands" per *Merriam-Webster*) are taught to be of any nature, including proteins, peptides oligonucleotides, DNA plasmids [0056], anti-infectious agents and antibiotics [0052], or anticancer agents such as busulfan ([0053] and Example 4). Heurtault further teaches the preparation of an aqueous emulsion (Abstract) of which the colloidal particles are the lipid nanocapsules [0010].

Heurtault does not teach the use of a phospholipid derivative of polyethylene glycol (PEG) in the outer lipid coating. The percent ranges of the outer lipid envelope dedicated to lipophilic and hydrophilic surfactants are not taught. Circulatory duration lasting two hours or longer is also not taught. Specific amphiphilic anticancer agents such as doxorubicin and paclitaxel or Taxol® are not taught nor are specific anti-infectious agents such as amphotericin B. Lecithin comprising 95% or 99% or greater of phosphatidylcholine is not taught. However, in view of The Merck index (see pp. 711-712), one of ordinary skill in the art would have been motivated to optimize lecithin such that it would comprise equal to or greater than 99% phosphatidylcholine in light of the reference teaching the two compounds as being synonymous with one another or 100% equivalent.

Önyüksel teaches nano-sized sterically stable micelles (SSMs) and liposomes (SSLs) having a hydrophobic cores which contain at least one lipid component and,

preferably, in combination with or association with an amphiphilic derivative of PEG comprising a molecular weight between 1000 and 5000 and a preferred hydrophobic component such as distearoyl-phosphatidylethanolamine (i.e. DSPE-PEG_{5000}) (col. 16, lines 1-45). Half-lives of the liposomes in the blood (i.e. circulation time) are taught as controllable by adjusting such properties of the PEG component of the amphiphilic surfactant as molecular weight (e.g. PEG_{2000} versus PEG_{5000}), chain length, and concentration (col. 7, lines 26-43). Önyüksel further teaches the micelle as being biologically active wherein an agent may, for example, possess anti-cancer activity (e.g. Taxol® or doxorubicin), anti-inflammatory activity (e.g. prednisone), or anti-microbial activity (e.g. amphotericin B) (claims 17 and col. 16, lines 1-12).

Önyüksel lacks teaching the specific mol percentage ranges of amphiphilic derivative that comprise the outer lipid envelope, teaching the specific mol percentage ranges of hydrophilic surfactant that comprise the outer lipid envelope, and teaching a liposomal half-life in the blood of at least 2 hours.

In view of the combined teachings of the prior art, one of ordinary skill in the pharmaceutical or biomedical device art would have been motivated to include a DSPE-PEG derivative such as DSPE-PEG_{5000}, in the hydrophobic, lipid-core nanocapsule composition as practiced by Heurtault with a reasonable expectation of successfully preparing nanocapsules having increased stability and duration. Such would have been obvious in the absence of evidence to the contrary since the inclusion of amphiphilic derivatives such as DSPE-PEG in nanocapsules are shown to confer increased circulation time within the body as taught by Önyüksel (col. 16, lines 30-45). Both references teach

the inclusion of anti-cancer agents, and ant-infectious or anti-microbial agents, but Önyüksel's teachings of these drug types specifically exemplify such drugs as Taxol®, doxorubicin or amphotericin B, all of which are well known and deemed obvious to one of ordinary skill in the art.

Neither of the references teach the specific mol percentage ranges of amphiphilic derivative, lipophilic surfactant or hydrophilic surfactant that comprise the outer lipid envelope, or a compositional half-life in the blood of at least 2 hours, as instantly claimed by Applicants. Since parameters with respect to the claimed composition such as the molecular weight, chain length and concentration of PEG (Önyüksel, col. 7, lines 26-43 and col. 16, lines 30-45) are adjustable, it follows that each is a result-effective parameter that a person having ordinary skill in the art would routinely optimize in order to best achieve the desired mol percentage of amphiphilic derivative best suited to optimizing the circulation time of the nanocapsule composition. Similarly, adjustments to optimize the mol percentages of both the lipophilic and hydrophilic surfactants within the bioactive nanocapsules are well within the purview of the skilled artisan and would further motivate said artisan to optimize size, release and stabilization properties said bioactive nanocapsule compositions (Heurtault [0037]-[0042]). Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. Thus, absent some demonstration of unexpected results from the claimed parameters, optimization of any of these parameters would have been obvious at the time of Applicant's invention.

No claims allowed.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey T. Palenik whose telephone number is (571) 270-1966. The examiner can normally be reached on 7:30 am - 5:00 pm; M-F (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jeffrey T. Palenik/
Examiner, Art Unit 1615

/MP WOODWARD/
Supervisory Patent Examiner, Art Unit 1615